

U.S. Appl. No. 10/813,745
Attorney Docket No. P-162-US1
Page 13 of 17

II. REMARKS

Applicants respectfully request reconsideration of this application in view of the above amendments and the following remarks.

1. Status of the Claims

Claims 1-40 were originally pending in this application. Claims 1-18, 20, 30 and 32-40 have been canceled. Accordingly, Claims 19, 21-29 and 31 are pending for examination on the merits.

2. Summary of the Amendments

Claims 1-18, 20, 30, and 32-39 have been canceled without prejudice or disclaimer. In view of these cancellations, the claim dependencies for Claims 21-23, 25-27, 29 and 31 have been amended. Entry of these amendments is respectfully requested.

3. Rejections Under 35 U.S.C. §112, First Paragraph

Claim 19 has been rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable any person skilled in the art to make or use the invention commensurate in scope with the claims. Specially, the Examiner has indicated that "the specification, while being enabling for compounds wherein R4 is alkylene, does not reasonably provide enablement for R4 being all other R4 moieties...." (Office Action dated February 13, 2007, at page 3). Applicants respectfully traverse this rejection for the following reasons.

A patent application is presumptively enabled when filed. More specifically, during examination, "[a]s a matter of Patent Office practice . . . a specification . . . must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d at 223, 169 U.S.P.Q. at 369. Moreover,

U.S. Appl. No. 10/813,745
Attorney Docket No. P-162-US1
Page 14 of 17

... it is incumbent upon the Patent Office, whenever a rejection on [grounds of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. *Id.* at 224, 169 U.S.P.Q. at 369-70.

Thus, the Examiner bears the initial burden of establishing a *prima facie* case of non-enablement which must be supported by acceptable evidence or reasoning. In the present case, the Examiner has not established a *prima facie* case of non-enablement because the Examiner's evidence and reasoning is either inaccurate or not relevant for the presently claimed subject matter.

A. Examiner Has Not Established Non-Enablement for How to Make the Claimed Invention

The present specification provides nine general synthetic procedures useful for preparing the presently claimed compounds on, for example, page 47, line 16 to page 52, line 11. Representative reaction conditions for each of these general synthetic procedures, such as reaction temperatures, times, diluents, reagents, etc., are also described on page 52, line 16 to page 60, line 29. Additionally, the present specification provides over one-hundred detailed preparations and examples on page 79, line 01 to page 127, line 10, that describe how to prepare the presently claimed compounds.

The Examiner has challenged the adequacy of these teachings of how to make the claimed compounds with the following statements:

The only examples provided by the instant specification, namely examples 1-20 have R4 being alkylenylene [sic] which is optionally substituted. The closest prior art is where the equivalent to the instant R4 is alkylene of 1-3 carbon atoms. It is not seen where the instant specification teaches how to make use or choose R4 moieties other than alkylene. Office Action dated February 13, 2007, at page 3.

U.S. Appl. No. 10/813,745
Attorney Docket No. P-162-US1
Page 15 of 17

The compounds made by the instant specification have only R⁴ being alkylene of up to 10 carbon atoms. The specification speaks of Table I and Table II which have more examples (up to 300 more examples) of compounds made by the instant specification, but the instant specification does not contain tables I or II. Office Action dated February 13, 2007, at page 7.

These statements are factually incorrect.

For example, the Examiner contends that Examples 1-20 only give examples of R⁴ as optionally substituted alkylene and "[i]t is not seen where the instant specification teaches how to make, use or choose R⁴ moieties other than alkylene." However, Examples 3-11 and 20 clearly teach how to prepare compounds where R⁴ contains an amide. Similarly, in Examples 12 and 13, R⁴ contains a sulfonamide; in Example 14, R⁴ contains a urea; in Example 15, R⁴ contains an amine; and in Example 17, R⁴ contains an ether. Additionally, in Examples 5, 6, 11, 13-18 and 20, R⁴ contains an arylene group; in Examples 9 and 10, R⁴ contains a cycloalkylene group; in Example 16, R⁴ contains a heterocyclene group; and in Example 19, R⁴ contains a heteroarylene group. Thus, the Examiner statements are clearly not supported by the facts.

Applicants further note that Tables I and II, which the Examiner indicates are not contained in the specification, are actually found on page 31, line 11 to page 41, end of page. Thus, this statement is also factually incorrect.

The Examiner has provided no other assertions regarding the inadequacy of the application relating to how to make the presently claimed invention. Accordingly, the Examiner has not established a *prima facie* case of non-enablement for how to make the presently claimed invention because the Examiner has not provided any acceptable evidence or reasoning to support a finding of non-enablement.

U.S. Appl. No. 10/813,745
Attorney Docket No. P-162-US1
Page 16 of 17

B. Examiner Has Not Established Non-Enablement for How to Use the
Claimed Invention

The present application provides a number of uses for the presently claimed compounds, including treatment of medical conditions mediated by β_2 adrenergic receptors or muscarinic receptors (page 73, lines 04-06); treating pulmonary disorders (page 73, lines 14-15); providing bronchodilation (page 73, lines 21-22); treating chronic obstructive pulmonary disease or asthma (page 73, lines 28-29); and use as research tools for investigating or studying biological systems or samples, or for discovering new compounds having both β_2 adrenergic agonist activity and muscarinic receptor antagonist activity (page 75, lines 10-14).

The present application also provides detailed *in vitro* and *in vivo* assays demonstrating how to use the presently claimed compounds. For example, among other *in vitro* assays, the specification describes a radioligand binding assay for adrenergic receptors on page 128, line 20 to page 129, line 27; a radioligand binding assay for muscarinic receptors on page 129, line 29 to page 130, line 33; and a functional assay for adrenergic receptor activity on page 131, line 01 to page 132, line 08. Data for a representative compound of the present invention is also provided for each of these assays. The application also provides two detailed *in vivo* assays for determining bronchodilation in mammals. Thus, using these assays, a person of ordinary skill in the art could use the presently claimed subject matter without undue experimentation.

The Examiner has challenged the adequacy of the application primarily with regard to use of the claimed compounds for the treatment of medical conditions. In this regard, the Examiner has cited the alleged unpredictability of the pharmaceutical arts and the alleged lack of correlation between *in vitro* assays and clinically successful drugs. Applicants strongly disagree with the Examiner's assertions. However, in view of the fact that the method of treatment claims have been canceled in this application due to the restriction requirement, the issue of enablement of the method of treatment claims has been rendered moot. Accordingly, this rejection may be withdrawn.

For the foregoing reasons, Applicants respectfully request that the rejection of Claim 19 under 35 U.S.C. §112, first paragraph, be withdrawn.

U.S. Appl. No. 10/813,745
Attorney Docket No. P-162-US1
Page 17 of 17

4. Allowable Subject Matter


Applicants note with appreciation that the Examiner has indicated that claims drawn to compounds of formula III where R^4 is alkylene are allowable in view of the prior art.

III. CONCLUSIONS

Reconsideration of this application in view of the above amendments and remarks is respectfully requested. Should there be any questions regarding this paper, the Examiner is encouraged to telephone the undersigned attorney for Applicants at (650) 808-6406.

Respectfully submitted,
THERAVANCE, INC.

Date: April 19, 2007

By: 
Jeffrey A. Hagenah, Ph.D., Esq.
Reg. No. 35,175
Telephone No. (650) 808-6406

THERAVANCE, INC.
901 Gateway Boulevard
South San Francisco, CA 94080
Phone: (650) 808-6000; Fax: (650)-808-6078